UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,408	10/01/2003	Juergen Roemisch	6478.1446-01	5124

22852 7590 02/25/2008

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
02/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/674,408	ROEMISCH ET AL.	
	Examiner	Art Unit	
	SAMUEL W. LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-62* is/are pending in the application.

4a) Of the above claim(s) *nine* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09632974.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 33-62 are pending.

The amendment filed 12/5/07 which cancels claims 1-32 and 63-75 has been entered. The Applicants' request filed 12/5/07 for extension of time of one month has been entered. Claims 33-62 are examined in this Office action.

Withdrawal of the rejections

- The rejection of claims 63, 66-67, 69 and 73-75 under 35 USC 102(b) are withdrawn in light of cancellation of theses claims. But, the 102 rejection of the pending claims (see below) is maintained (see below)

- The rejection of claims 63-69 and 71-75 under 35 USC 103(a) by Choi-Miura et al. and Turner et al. are withdrawn in light of cancellation of theses claims. Yet, the 103 rejection of the pending claims (see below) is maintained.

Maintained- Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 33-62 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33 and 48 lack antecedent basis for "the protease"; this limitation does not indicate to which one (protease) the claims refer. The dependent claims are also rejected.

The applicants' response to the rejection under 35 USC 112, second paragraph

At page 8, 1st paragraph, the response filed 12/5/07 argues that the word "the" in the phrase "the protease …" does not renders the claims indefinite as the phrase is used in the title and repeatedly throughout the application (see page 11, 2nd paragraph).

The applicants' argument is found unpersuasive because claims 33 and 48 lack antecedent basis for "the protease" in the pending claims regardless of its use in the title or in the Spec.

Maintained-Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description

Claims 33-62 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 33 and 48 are directed to composition comprising a precursor of protease (proenzyme) (claim 33) and both of the protease and the proenzyme (claim 48), respectively. The genus of the proenzyme polypeptide of claims 33 and 48, and the genus of protease polypeptide of claim 48 lack adequate written description for two reasons: 1) the full-length of amino acid sequences for the proenzyme and for the protease have not been described in the specification and in the claims; and 2) the open claim language ("… comprises the following

peptide sequences…."), reads on a large genus, only partial sequences (four oligopeptides of SEQID NOs:1-4) of which is adequately described. Claims 33 and 48 and the dependent claims therefrom are directed to polypeptides which are resulted from any random combinations (not in ordered sequence) of the four oligopeptide, e.g., tandem covalent linkages of any combination of the oligopeptides thereof. The genus of claims 33 and 48 lack adequate written description because the open claims language (directed to the partial sequences) reads on full-length proenzyme and the protease which are not adequately described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses SEQ ID NOs: 1-4 as subseqeunces of the proenzyme of a protease enzyme that activates blood clotting factor VII, or the protease which is post-

translationally processed from said proenzyme; however, none of these four sequences disclosed are full length polypeptides; they are only partial amino acid sequences.

The specification fails to teach (i) what is structural relation of these four oligopeptides to the full-length polypeptide of the proenzyme or/and the protease; (ii) whether or not these oligopeptides are all or only some of them are presented in the proenzyme or the protease. Without these teachings, the skilled artisan is unable to predict the full-length proenzyme or protease from the disclosed oligopeptide sequences (wherein the full-length polypeptide contains said sequences).

This is not to say that applicants have not enabled one of skill in the art to obtain the full length polypeptide sequences using well-known PCR-cloning technology via primers derived from these sequences to clone out gene encoding the proenzyme and thus to obtain the peptide sequence thereof; this is to say that applicants have not described, directly or predictably, the sequences of the full-length proenzyme and full-length protease. Given the limited disclosure of structurally described species and the unpredictability of the art, applicants have failed to adequately describe a representative species of the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention, i.e., the composition comprising the full length polypeptides.

Moreover, since applicants do not fully describe a single full length polypeptide of any of the proteases (which *directly* or *indirectly* activate the factor VII), the addition of functional language in the instant claim, along with the retention of instant comprising language so as to read on the full length polypeptides, would not correct the defect of the instant claims because, to have adequate written description, the instant specification must contain a fully described,

representative species (the full-length amino acid sequences) of the claimed genus as well as structure/function relationships between said fully described species and the other members of the genus.

Therefore, the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Enablement rejection

Claims 33-62 remain are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 33 and 48 are directed to composition comprising a precursor of protease (proenzyme) (claim 33) and both [mixture] of the protease and the proenzyme (claim 48), respectively. The instant specification fails to teach the full-length amino acid sequence of the proenzyme polypeptide of claim 33 and the full-length amino acid sequence of the activated protease of claim 48. The claims and the specification only disclose partial sequence, i.e., four oligopeptides of SEQID NOs:1-4). The instant specification discloses SEQ ID NOs: 1-4 as subseqeunces of the proenzyme of a protease enzyme that activates blood clotting factor VII, or the protease which is post-translationally processed from said proenzyme; however, none of these four sequences disclosed are full-length polypeptides; they are only partial amino acid sequences. Also, the specification does not provide guidance or direction as to (i) what is structural relation of these four oligopeptides to the full-length polypeptide of the proenzyme

or/and the protease; (ii) whether or not these oligopeptides are all or only some of them are presented in the proenzyme or the protease. Without the guidance or direction, the skilled artisan is unable to predict the full-length proenzyme or protease from the disclosed oligopeptide sequences (wherein the full-length polypeptide contains said sequences).

The instant disclosure does not satisfy enablement requirement of 35 U.S.C. §112, since without the full-length sequence, one skilled in the art is unable to make and use the claimed composition which requires the full-length sequences thereof. Claims 33 and 48 and the dependent claims therefrom are directed to polypeptides which are resulted from any random combinations (not in ordered sequence) of the four oligopeptide, e.g., tandem covalent linkages of any combination of the oligopeptides thereof. The open claims language (directed to the partial sequences) reads on full-length sequences of the proenzyme and the protease are not adequately described in the specification. Thus, the outcome of making functional proenzyme and the protease is unpredictable, and breath of the instant disclosure is broad than that is enabled, which do not allow one skilled in the art to make and use the claimed composition.

Without knowing the amino acid sequences for the above indicated the proenzyme and the protease thereof, one skilled in the art is unable to identify and characterized biological activity of the proenzyme and protease thereof, thereby to make and use the claimed composition comprising the proenzyme and the protease.

Scope enablement

Claims 48-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the composition comprising proenzyme of a protease that activates

blood clotting factor VII (not mixture with proprotease thereof), does not reasonably provide ennoblement for the composition comprising both purified proenzyme thereof and the catalytically active protease (which is processed from precursor, i.e., the proenzyme). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the ennoblement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor applicable is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/(2) The nature of the invention:

Claims 48-62 are directed to a composition comprising a purified proenzyme and protease which is enzymatically processed from the proenzyme thereof. The specification does not teach nor provide working example(s) for purification of the active protease. Although there provides example for chromatographic purification for the *proenzyme* (page 10), the instant specification fails to teach or/and provide working example for purifying the enzymatically active *protease* thereof. The specification sets forth that the amino acid sequence of the protease

has 100% sequence identity to that of the protein taught by Choi-Miura et al. (see page 1, the last three lines). Choi-Miura et al., however, teach that their PHBP protein is a heterodimer consisiting of 50 and 17 KDa subunits (see abstract). Thus, chromatographic behaviors between the protease (heterodimer) and the proenzyme (non-dimer form) would be distinct/different. Since the purification mean set forth in specification (page 10) is applied to the proenzyme, the outcome of purifying the heterodimer form of the protease (mature form) is not predictable. This renders the instant claims not enabled to the full extent of their scope without undue experimentation.

The composition of claims 48-62 requires the presence of both (mixing) the protease and the proenzyme simultaneously. However, the specification fails to teach how to prevent the activating (a proteolysis process) the proenzyme *via* specific cleavage of the proenzyme, assuming that the mature form, i.e., active protease which is processed from the proenzyme has ability of activating the proenzyme thereof. The example for this is that chymotrypsin can enzymatically act on chymotrypsinogen (see below in *section* (3) for the detail). Thus, a great deal of experimentation is needed to characterize the condition so as to allow for formulation of the proenzyme and the protease together without unpredictable "activation" or degradation of the proenzyme (the components of the claimed composition).

Furthermore, since the specification does not describe the full-length sequence of said protease, one skilled in the art would have construed that the protease mentioned in the specification (the third line from the bottom at page 1) is the matured protease but not the proenzyme (this is because that the specification has clearly used the term "proenzyme" throughout the instant disclosure to distinguish from the term "protease"). When characterizing

the enzymatic activity of the protease, one would have hardly found activity inasmuch as said protease is inactive as being a proprotease. Hence, identifying property and function of the purified, in this regard, also requires undue experimentation.

(3) The unpredictability of the art:

It has been well-known that proprotease (proenzyme), e.g., chymotrypsinogen (a proenzyme) can be self-cleavage by protease that is processed from proprotease, e.g., chymotrypsin (see page 2685, the right column, lines 9-14, Velev et al. *Biophy. J.* (1998) 75, 2682-2697). Since the specification fails to teach processing (activating) the claimed proenzyme to the active protease, the outcome of "mixing" of the proenzyme and the protease together (claim 48) is highly unpredictable (in view of that the protease will "activate" the proenzyme in the composition to produce the protease, which 'activation" would eventually result in no proenzyme coexistence with the activated protease). Therefore, stability and property of the claimed composition comprising both the proenzyme and the protease is unpredictable.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attribute and characteristics that identify (i) functional composition comprising both the proenzyme and the protease (wherein the proenzyme will not be enzymatically degraded by the protease), and (ii) parameters for purifying the active protease, the instant specification needs to provide omitted teaching or description in this regard in order for enabling the claimed invention.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to purifying the active protease and preparing the composition containing both the proenzyme and the protease, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable (see above). One skilled in the art would have been required to carry out undue experimentation for finding out proper mean to purify the bioactive protease and for screening and characterizing the composition that allows for productive formulation of both proenzyme and the protease together under the condition(s) that said protease does not activates or degrade the purified proenzyme.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of peptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in enzymology and protein purification as well as knowledge in protein chemistry. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. An unduly level of skill is needed for the skilled artisan in order to make and characterize the above-discussed composition comprising the proenzyme ad the protease, and develop a mean for purifying the enzymatically active protease.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and

the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Thus, the amount and level of experimentation needed is undue.

The applicants' response to the rejection under 35 USC 112, first paragraph

At pages 9-12, the response filed 12/5/07 discusses the lack of written description of the instant claims via citing several cases/case laws. The response argues that the "partial sequences" (four oligopeptides of instant SEQ ID NOs:1-4) of the claimed proenzyme (proprotease) of the protease that activates blood clotting factor VII or the claimed protease thereof meets the written description requirement, and asserts that the partial sequences may be used to confirm the identity of bands of protein obtained (page 12, 2nd paragraph). Thus, the response request withdrawal of the rejection.

The applicants' arguments are found unpersuasive becasue of the reasons which have been well-discussed in the above rejection (written description), and the reasons below. It should be noted that the Examiner is not charged with comparing and contrasting claims under examination with claims found in case law. Rather, the Examiner analyzes the claims with respect to the statute with the aid of the written description guidelines that he has been provided. The four oligopeptide sequences, i.e., "partial sequences" cannot represent the genus of the proprotease or protease polypeptide, the Spec fails to describe full-length structure thereof and fails to teach structure ("partial sequences")-function correlation thereof, and thus fails to satisfy the written description requirement under 35 USC 112. Use of the "partial sequences" to confirm the identity of bands of protein obtained as asserted by the response per se does not provide any factual indicia for the adequate written description herein. The genus of claims 33 and 48

proprotease and protease polypeptide are therefore deemed to lack adequate written description. Therefore, the rejection is proper and maintained.

From page 13-14, the response discusses the enablement issue of the instant claims. The response submits that the German patent application (to which this applicant claims foreign priority) and prior art have taught the method of testing the activity of the claimed protease and proenzyme ("proprotease"), and thus, there is no need for further information to satisfy the enablement requirement (page 13, last paragraph to page 14, 1st paragraph). Also, the response discusses the mixture of the proprotease and protease thereof, and asserts that, the Spec at page 6 teaches that the proprotease remains intact by carrying out the purification method under acidic pH, and exposing the purified proenzyme to a higher pH would gradually allow for self-cleavage and re-exposing the purified proenzyme to a lower pH would stabilize the proprotease (proenzyme) form (page 14, 2nd paragraph). Based on this argument, the response infers that the Spec is enable for the mixture of the proprotease and protease, and therefore, request withdrawal of the enablement rejection.

The applicants' arguments are found unpersuasive because of the reasons set forth in the above rejection, and reasons below. The Spec only discloses the four oligopeptides, i.e., "partial sequences" without teaching the full-length sequences of the proprotease/protease. Neither the Spec nor the relative art (including the German patent application) provides (i) guidance or direction as to structural correlation of the "partial sequences" with the full-length polypeptide of, and (ii) whether or not al or some of these "partial sequences" are presented in the proprotease or/and protease. Thus, one skilled in the art is unable to make and use of the claimed composition. Page 6 of instant Spec only teaches that "it is possible under the acidic condition to

obtain, from a solution containing the proenzyme, an eluate which contains the proenzyme". However, the Spec does not clearly teach lower pH condition can stabilize proenzyme (proprotease) in the "eluate", i.e., "a mixture" or solution containing both the proenzyme and active protease thereof, nor provide any working example or factual indicia in this regard. The spec does not teach that exposing the purified proenzyme to a higher pH would gradually allow for self-cleavage. The page 6 teaching of the Spec discussed above can be regarded as a condition for purifying the proenzyme at "a high yield" (see page 6, line 18 of the Spec) not necessarily refers to lower pH stabilizing the proenzyme or/and higher pH promoting proteolysis of the proenzyme by "mixed" protease thereof. Moreover, actual pH has not been provided by the Spec or the relative art becasue "lower pH" is broad genus; and thus, further guidance in this regard may be required for enabling the full scope of the claimed compositions. The art in this field teach that proprotease polypeptide is self-cleaved and inactivated by the protease thereof (see page 9-10 of the Office action mailed 8/6/07). Therefore, the Spec does not enable for the mixture of the proenzyme and the protease disclosed in claims 48-62, and therefore, the enablement and scope enablement rejections are proper and maintained.

* Examiner note that claims 48 and the dependent claims therefrom are not rejected in the 102 rejection and 103 rejection because of the "enablement" issue discussed above.

Maintained-Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33, 39 and 45-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Choi-Miura et al. (*J. Biochem.* (1996) 119, 1157-1165).

Choi-Miura et al. teach the purified 560 amino acid hyaluronan-binding protein (PHBP) polypeptide comprising the instant amino acid sequences of SEQ ID NOs: 1-4 (see Figure 3) in a chromatographic eluent (i.e., composition) (see left column, 2nd paragraph, page 1161). Because the PHBP protein is purified by affinity chromatography shown by a single 70 KDa band on SDS-PAGE (see page 1161, 2nd paragraph, line 12), the purified PHBP is in pure form, wherein active form of this PHBP has *inherent* serine protease activity and said 70 KDa band refers to proenzyme (see "Discussion of art"). Further, Choi-Miura et al. teach the eluent (composition) comprising the purified PHBP from HA-Sepharose column contains glycine (see page 1161, left column). Therefore, Choi-Miura et al. teach the composition of claim 33.

Since claims 39 and 45 are drawn to the composition comprising amino acid(s), e.g., glycine, the above Choi-Miura et al. teachings anticipate claims 39 and 45.

The above-discussed eluent contains mini-amount albumin (see page 1162, the left column), which anticipates claim 46.

Since the recitation of claim 47 "*composition acts as a biological test reagent*" is considered to be an intended use which has no patentable weight, the above Choi-Miura et al. teachings anticipate claim 47.

The applicants' response to the rejection under 35 USC 102

At pages 15-16, the response filed 12/5/07 submits that Choi-Miura et al. does not teach purifying any particular form of the protein. This reference simply teaches extracting the protein from blood plasma in two or more bands (page 15, the 2nd paragraph). The response asserts that page 1159, Figure 1(b) of the article depicts the N-terminal sequences of the 50 kDa and 17 kDa bands of the protein. The response asserts that if Choi-Miura et al. have isolated the proenzyme, one of these N-terminal sequences should be the proenzyme sequence; yet, they do not. Thus, the response asserts that Choi-Miura et al. obtained only protease or its fragment not the proenzyme (page 15, 3rd paragraph). Also, the response discusses "sequence 1 and 2" which do not contain the N-terminal leader sequence (i.e., signal peptide) of Figure 6, and submits that 17 KDa band is a portion of the cleaved protease (page 15, last paragraph). Hence, the response infers that Choi-Miura et al. do not teach the elements of the instant claims and request of withdrawal of the rejection.

The applicants' arguments are found unpersuasive because of the reasons below. Choi-Miura et al. teach that resulting eluate gave a single band of 70 KDa called "PHBP" (Fig.1, a-2, lane 1) (see page 1161, left column, 2nd paragraph 1ines 11-13). Choi-Miura et al. clearly teach the "PHBP precursor", has the same sequence of the proenzyme depicted in Figure 6 (see page 163, right column, 2nd paragraph). Moreover, the instant page 1 (the last three lines) of instant Spec explicitly sets firth that the protease sequence of Choi-Miura et al. has sequence identity 100% with the instant sequence. This indicates that the polypeptide disclosed by Choi-Miura et al. is the same proenzyme disclosed by instant application, and that the "70 KDa" polypeptide is the proenzyme thereof. Thus, Choi-Miura et al. teach the instant proenzyme and composition comprising the proenzyme thereof, and therefore, the rejection is maintained.

Maintained-Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-36, 38-39 are 42-47 are again rejected under 35 U.S.C. 103(a) over as obvious over Choi-Miura et al. (*J. Biochem.* (1996) 119, 1157-1165) in view of Turner et al. (US Pat. No.5326558).

The rejection of claims 33, 39 and 45-47 by Choi-Miura et al. has been discussed above.

Choi-Miura et al. do not expressly teach that the composition comprises complexing agent (e.g., EGTA or EDTA), and compound (e.g., aprotinin) for preventing protein degradation.

Choi-Miura et al. have taught that the purified PHBP is suspectable to cleavage by proteolytic enzymes (see page 1162). It is well known that EGTA or EDTA and protease inhibitor compound, e.g., aprotinin, are routinely used in the protein purification procedure to prevent the purified protein/enzyme from proteolytic degradation. Turner et al. teach a cocktail

comprising protease inhibitors (aprotinin, leupeptin, EGTA) which was added to the sample containing the protein that is subject to purification in order to minimize proteolysis (see column 13, lines 2-8), which is applied to claims 34-36, 38 and 43-44. It is well know in the art that isolation of active enzymes or proteins using buffer that contains reductant, e.g., dithiothreitol or mercaptoethanol to reduce or prevent sulfhydryl oxidation, as applied to claim 42.

One of ordinary skill in the art at the time the invention was made would have been motivated to formulate the composition with the above-mentioned protease inhibitory compounds. This is because Choi-Miura et al. already stated the problem regarding degradation of PHBP protein by the proteolytic enzyme, and because those protease inhibitory compounds are known and routinely used by the skilled artisan in order to reduce or minimize the proteolysis of protein of interest (here it is the purified PHBP), as is noted by Turner et al. reference.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

The applicants' response to the rejection under 35 USC 103(a)

At pages 16-17, the response filed 12/507 argues again against the Choi-Miura et al. with regard to pure form of the protease or the proenzyme, and assert that Choi-Miura et al. were unable to obtain to the proenzyme (page 17, 1st paragraph). The response asserts that the experimental condition (e.g., pH) set forth in Example 2 of instant application allows for purifying a proenzyme form of the protease (page 17, 2nd paragraph). Also, the response argues that Turner et al. do not pertain to the instant proenzyme or protease nor suggests the elements of claims 33-62. Thus, the response requests withdrawal of the rejection.

The applicants' arguments are found unpersuasive because of the reasons set forth above and the reasons below. Te primary reference Choi-Miura et al. has taught the purified proenzyme called "PHBP" identical to instant proenzyme (see the above discussion of the applicants' response to 102 rejections). Choi-Miura et al. teach purification "PHBP" under acidic pH condition (see page 1161, left column, 2nd paragraph lines 3-4) which the applicant submits to be essential for obtaining intact proenzyme. Turner et al. teaching provides the factual indicia as to the routine use of the protease inhibitors, e.g., EDTA during protein/enzyme preparation or/and purification. Thus, the rejection is deemed proper and stands.

Conclusion

No claims are allowed.

Discussion of the art

The prior art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

• McIntyre et al. (*J. Biol. Chem.* (1994) 269, 567-572) teach that proenzymen of protease procathepsin lacks the signal peptide, indicating that proenzyme may not necessarily contain the signal peptidesequence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon, can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

/Samuel W Liu/
Examiner, Art Unit 1656
February 15, 2008

/Karen Cochrane Carlson, Ph.D./
Primary Examiner, Art Unit 1656